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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/851,327	05/09/2001	Robert J. Levy	047172-0170	2799

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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/18/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/851,327	Levy et al.
Examiner	**Art Unit**
Scott D. Priebe, Ph.D.	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 25, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above, claim(s) *2, 6, 10, 11, 13, 17, 19, 20, 22-25, and 29-31* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3-5, 7-9, 12, 14-16, 18, 21, 26-28, 32, and 33* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 6
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restriction

Applicant's election with traverse of Group A3, claims 1, 3-5, 7-9, 12, 14-16, 18, 21, 26-28, 32 and 33 as directed to tenascin C and/or thymosin β4 (TB4) in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the separate inventions are related and require no separate search. This is not found persuasive because while the inventions are related by ultimate effect, they are not related by the means for achieving that effect. The different agents of the different inventions do not share either structural or functional features with one another. Clearly, a search of each of the different agents would be different form a search of the other agents, and would not require a search of the other agents. For example, a search to determine whether tenascin C had been used to enhance transfection would not necessarily uncover any art on whether TB4 had ever been used; and indeed it did not. The invention as directed to tenascin C is anticipated by Schneider et al., which makes no mention of the other agents listed in the claims, except perhaps for a modulator of an integrin which mediates the tenascin C - TB4 pathway. Tenascin C and TB4 were grouped together because claim 9 recites a combination of the two agents. The invention directed to one of these agents alone was not distinct from the combination, and restriction between them would be improper. These two agents were not grouped together because of any mechanistic relationship, as surmised by Applicant. With respect to the alleged mechanistic relationship, this is speculation on Applicant's part and has not

been directly tested. For example, the effect of tenascin C has not been tested in cells deficient in thymosin β4. Also, there is no evidence that modulation of proteins, such as ras and raf, which are involved in many different signaling pathways would always induce expression of TB4 or result in enhanced transfection.

The requirement is still deemed proper and is therefore made FINAL.

Claims 2, 6, 10, 11, 13, 17, 19, 20, 22-25, and 29-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9, filed 10/25/02.

Priority

If applicant desires priority under 35 U.S.C. 119(e) based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

If the application is a utility or plant application filed on or after November 29, 2000, any claim for priority must be made during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2) and (a)(5). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). Indication of a priority claim in the oath or declaration does not meet this requirement. A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) a surcharge under 37 CFR 1.17(t), and (2) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Commissioner may require additional information where there is a question whether the delay was unintentional. The petition should be directed to the Office of Petitions, Box DAC, Assistant Commissioner for Patents, Washington, DC 20231.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-5, 7-9, 12, 14-16, 18, 21, and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for enhancing transfection of cultured cells with cationic liposomes comprising plasmid by growth in the presence of tenascin C before, during, or after transfection, does not reasonably provide enablement for any other embodiments embraced by claims 1 and 27. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. Claims which are generic to the agent are examined only with respect to the agent being tenascin C or TB4 (or both).

The claims are directed to a method for enhancing transfection either *in vitro* or *in vivo* by providing an "agent capable of enhancing the cytoskeletal permissiveness of said cell for transfection." Based on three working examples performed with cultured vascular smooth muscle cells, Applicant speculates that the enhanced transfection was due to "increasing the cytoskeletal permissiveness for transfection." Growth of the cells on denatured collagen (gelatin) or with tenascin C before and after transfection, or in the presence of cytochalasin D after transfection with cationic liposomes comprising plasmid DNA were observed to have an enhancing effect on transfection. No working examples with other agents are provided, nor of transfection *in vivo*. The guidance provided by the specification is minimal with respect to selection of agents which could be expected to increase "the cytoskeletal permissiveness for transfection," or how such agents would be provided to cells, particularly *in vivo*.

The only criterion disclosed for identifying "enhanced cytoskeletal permissiveness" *a priori* is whether the actin depolymerization results. Denatured collagen and tenascin C induce expression of TB4 in the smooth muscle cells. TB4 is an actin binding protein which sequesters G-actin, and thus driving actin polymerization/depolymerization in the favor of depolymerization. Applicant has proposed that any agent which lead to the depolymerization of actin in general should enhance transfection. Cytochalasins bind the end of an actin fiber to prevent further polymerization, which may lead to fragmentation of actin filaments. (It is not known to cause depolymerization *per se* as suggested in the specification.) No experimental results are described which confirm that the results observed were in fact due to the effect of the agents on cytoskeletal changes. For example, determining whether tenascin C or denatured collagen required an active TB4 gene in the target cell in order to enhance transfection. Matrigel is known to induce expression of TB4 (Grant et al., J. Cell Sci. 108 (Pt. 12): 3685-3694, Dec. 1995). However, growing cells on Matrigel before or during transfection leads to a decrease in transfection efficiency (Shih et al., Biotechniques 18 (5): 813, 814, 816, May 1995; and Pasco et al., DNA 8 (7): 535-541, Sep. 1989), which contradicts the speculation that induction of TB4 would improve transfection. Also, exposure of cells to a cytochalasin prior to transfection with cationic liposomes is known to inhibit transfection (Watanabe et al., J. Biochem. 116 (6): 1220-1226, Dec. 1994), which contradicts the speculation that blocking actin polymerization (at least before transfection) would enhance transfection.

With respect to the agent being TB4 itself, There is no guidance as to how TB4 would be effectively delivered to the cell. Unlike denatured collagen and tenascin C, which act at the cell surface, TB4 is a cytosolic protein. Unlike cytochalasins, proteins are not freely diffusible across a cell membrane. While methods are known for introducing proteins into cells, these methods are not used in conjunction with transfection, and there is no evidence of record that such methods could deliver TB4 in a manner that would allow enhancement of transfection, as opposed to inhibiting transfection. Consequently, it is left entirely to one of skill in the art to develop a method to effectively deliver TB4 to cells in conjunction with transfection such that transfection would be enhanced.

With respect to transfection *in vivo*, the claims require that transfection with the agent be enhanced over absence of the agent. As indicated above, there are no relevant working examples of *in vivo* transfection. Nor is there any guidance as to how the agent should be administered to cells *in vivo* in a manner such that transfection is enhanced relative to the absence of the agent. Orkin et al. reviews the infant state of the art of gene therapy from before the instant invention was made. The overall conclusions were: 1) gene therapy for each disease would present its own scientific and clinical challenges; 2) no successful gene therapy protocol was known; 3) significant problems remained in all aspects of gene therapy, especially with respect to effective expression vectors; 4) the pathophysiology of diseases to be treated were poorly understood; 5) one cannot predictably extrapolate the result of one animal model, such as mouse, to treatment of a disease in a different animal, such as human; 6) assessment of known gene therapy protocols

was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor definition of biochemical or disease endpoints; and 7) that gene therapy has been oversold, and the impression that gene therapy is successful is mistaken (pages 1-2). The specification (page 1)acknowledges, citing Orkin, that effective delivery of genes *in vivo* was hampered by a "dearth of effective gene transfer vectors." As indicated in Orkin, pages 8-10, transfection with naked DNA or DNA-liposomes is substantially lower in efficiency than are viral vectors; and the efficiency with viral vectors, generally, is not high enough. The instant invention is aimed at overcoming this particular problem. However, there is no evidence of record that the claimed invention would improve transfection efficiency *in vivo* at all, much less improve it enough to overcome this problem.

Therefore, in view of state of the art, the high unpredictability of *in vivo* transfection, the lack of relevant working examples for *in vivo* transfection, the lack of guidance commensurate in scope with the claims, and the amount and nature of the experimentation required to develop those embodiments of the invention for which guidance and examples are lacking, it would require undue experimentation to practice the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 recites that the cytoskeletal permissiveness for transfection is accomplished by "reducing the overall electronegative charge of the milieu surrounding [the cell] or the cytoplasm of said cell." It is unclear what this phrase means. In an aqueous solution, such as a cell culture, there is no "overall electronegative charge." While the surrounding media may have a negative potential relative to the cytoplasm, or *vice versa*, the overall charge is neutral. Furthermore, reducing the negative charge of the media would increase the negative charge of the cytoplasm and *vice versa*. Thus the alternatives recited are mutually exclusive, and opposite in nature. With respect to claims 15-16, it is unclear how increasing G-actin or depolymerizing F-actin would change the electronegative charge as required by the claims. Actin depolymerization is not known to generate or consume electrons. Consequently, it is unclear how the limitations of claims 14-16 limit the scope of claim 1.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 8, 12, 14-16, 21, 26-28, 32, and 33 are rejected under 35 U.S.C. 102(a) as being anticipated by Schneider et al. (FEBS Letters 458 (3): 329-332, 24 Sept. 1999).

Schneider discloses a method for enhancing transfection with a nucleic acid delivery system by providing a composition comprising a plasmid expression vector and a tenascin C peptide (PLAEDGIELTY). See entire reference, especially page 329, Abstract and col. 2, first para. With respect to claim 26, the tenascin C peptide appears to be a synthetic extracellular matrix molecule, since tenascin C is an EM protein.

While the reference does not describe the cellular processes that occur upon binding of the tenascin C peptide to its receptor, the specification discloses that tenascin C to its receptor binding results in induction of TB4 and favoring actin polymerization. Absent evidence to the contrary, the binding of tenascin C peptide to the tenascin C receptor, $\alpha_9\beta_1$, would presumably have these inherent effects. With respect to the kit, instructional material does not distinguish the claimed kit from the materials disclosed in the art, as it does not materially affect the use or function of those materials. *In re Gulack*, 217 USPQ 401 (CA FC 1983).

Claims 1, 4, 12, 14-16, 21, 26-28, 32 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Shih et al. (Biotechniques 18 (5): 813, 814, 816, May 1995), as evidenced by Grant et al. (J. Cell Sci. 108 (Pt. 12): 3685-3694, Dec. 1995).

Shih et al. discloses a method for enhancing transfection of primary hepatocytes with a plasmid by growth of transfected cells on Matrigel after transfection (but not before or during transfection). As disclosed in Grant et al., Matrigel induces TB4 expression, which presumably causes actin depolymerization, absent evidence to the contrary.

With respect to the kit, instructional material does not distinguish the claimed kit from the materials disclosed in the art, as it does not materially affect the use or function of those materials. *In re Gulack*, 217 USPQ 401 (CA FC 1983).

Claims 1, 3, 12, 14, 27,28 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Watanabe et al. (J. Biochem. 116 (6): 1220-1226, Dec. 1994).

Watanabe discloses a method of enhancing transfection of plasmid DNA by incorporating it into cationic liposomes. Watanabe discloses that the transfection is mediated by endocytosis, involving changes to the cytoskeleton that can be blocked by cytochalasin B. Consequently, the cationic lipid meets the limitation of enhancing "cytoskeletal permissiveness for transfection."

With respect to the kit, instructional material does not distinguish the claimed kit from the materials disclosed in the art, as it does not materially affect the use or function of those materials. *In re Gulack*, 217 USPQ 401 (CA FC 1983).

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX numbers are (703) 308-4242 or (703) 305-3014 for any type of communication. In addition, FAX numbers for a computer server system using RightFAX are also available for communications before final rejection, (703) 872-9306, and for communications after final rejection, (703) 872-9307, which will generate a return receipt. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on Monday through Friday from 8 AM to 4 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

Any inquiry concerning administrative, procedural or formal matters relating to this application should be directed to Patent Analyst Patsy Zimmerman whose telephone number is (703) 308-8338. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER